REMARKS

Prior to this response, claims 1 to 8 were pending and under examination. In the present communication, claim 1 has been amended. Claims 10 to 56 have been cancelled without prejudice. A marked-up copy of the amended claim to show changes made is included in Exhibit A, attached herewith. The claims as they will stand upon entry of the amendments is included in Exhibit B, attached herewith.

The amendments submitted herewith are supported by the specification and original claims and do not add new matter. The amendments do not require a new search or raise new issues for consideration because they merely address issues already raised by the Examiner or define Applicants' invention more clearly. It is submitted that the amendments place the claims in condition for allowance or in better condition for appeal by reducing the number of issues for consideration on appeal. The amendments were not made earlier in the prosecution because it is maintained that the previously pending claims were allowable. Since the amendments do not add new matter or require a new search or consideration, and place the claims in condition for allowance or in better condition for appeal, entry of the amendments is respectfully requested.

Objections to Claims

In response to the objection of claims 4 to 8 because claims 4 to 8 depend from rejected claims 1 and 3, it is respectfully submitted that amendment to claim 1 places the claim in condition for allowance. Thus, claims 4 to 8 may properly depend on claim 1. Accordingly, Applicant respectfully requests reconsideration and withdrawal of the objection.

Rejection Under 35 U.S.C. § 102(b)

The rejection of claims 1, 2 and 3 under 35 U.S.C. § 102(e) as being allegedly anticipated by Tsien *et al.* (United States Patent Number 5,981,200; hereinafter "Tsien") is respectfully traversed.

Applicants' invention, defined by amended claim 1, distinguishes over the art by requiring a fusion protein comprising a reporter polypeptide linked to a linker polypeptide comprising a protease cleavage site and a repressor polypeptide that represses the activity of said reporter polypeptide, wherein said repressor polypeptide is operatively linked to the linker polypeptide. Cleavage of the linker polypeptide at the protease cleavage site increases the activity of the reporter. The reporter polypeptide can be an enzyme, a transcriptional activator, or a polypeptide having at least one epitope.

In contrast, Tsien teaches a tandem fluorescent protein construct comprising a donor fluorescent protein moiety, an acceptor fluorescent protein moiety, and a peptide linker that couples the donor and acceptor fluorescent protein moieties. Tsien teaches only fluorescent protein moiety constructs containing two fluorescent protein moieties. Tsien does not teach or suggest using protein constructs containing a repressor protein and a reporter protein. Tsien does not teach or suggest a construct comprising an enzyme, a transcriptional activator or a polypeptide having at least one epitope. Indeed, Tsien does not teach or suggest a construct having any protein moiety other than fluorescent protein moieties. Therefore, Tsien does not anticipate Applicants' invention.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1, 2 and 3 under 35 U.S.C. § 102(e).

The rejection of claims 1 and 3 under 35 U.S.C. § 102(b) as allegedly being anticipated by Knight *et al.* (*Methods in Enzymology*, (1995) 248:18-34; hereinafter "Knight") is respectfully traversed.

Applicants' invention, as defined by amended claim 1, distinguishes over Knight by requiring a fusion protein comprising a reporter polypeptide linked to a linker polypeptide and a repressor polypeptide that represses the activity of the reporter polypeptide. Upon cleavage of the linker polypeptide at a protease cleavage site, activity of the reporter polypeptide is increased. The reporter polypeptide can be an enzyme, a transcriptional activator, or a polypeptide having at least one epitope. In contrast, Knight teaches constructs of fluorescent proteins and. as

acknowledged by the Examiner in the Office Action mailed December 5, 2001 (Paper No. 8), Knight teaches constructs that employ resonance energy transfer. Knight does not teach or suggest a construct comprising an enzyme, a transcriptional activator, or a polypeptide having an epitope. Indeed, Knight does not teach or suggest a construct comprising any non-fluorescent protein moiety. Therefore, Knight does not anticipate Applicants' invention.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(b).

In view of the above amendments and remarks, reconsideration and favorable action on all pending claims are respectfully requested. In the event any matters remain to be resolved in view of this communication, the Examiner is requested to telephone Lisa A. Haile, J.D., Ph.D., at (858) 677-1456 or the undersigned so that a prompt disposition of this application can be achieved.

Respectfully submitted,

Date: **October 3, 2001**

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Enclosures: Exhibits A and B

EXHIBIT A: CLAIMS WITH MARKINGS TO SHOW CHANGES MADE

1. (Amended) A fusion protein comprising:

b) a reporter polypeptide linked to a linker polypeptide comprising a protease cleavage site;

wherein said reporter polypeptide is an enzyme, a transcriptional activator, or a polypeptide having at least one epitope; and

b) a repressor polypeptide that represses the activity of said reporter polypeptide, wherein said repressor polypeptide is operatively linked to the linker polypeptide, and wherein cleavage of said linker polypeptide at said protease cleavage site increases the activity of said reporter.

EXHIBIT B: CLAIMS AS THEY WILL STAND UPON ENTRY OF THE AMENDMENTS

1. (Amended) A fusion protein comprising:

c) a reporter polypeptide linked to a linker polypeptide comprising a protease cleavage site;

wherein said reporter polypeptide is an enzyme, a transcriptional activator, or a polypeptide having at least one epitope; and

b) a repressor polypeptide that represses the activity of said reporter polypeptide, wherein said repressor polypeptide is operatively linked to the linker polypeptide, and wherein cleavage of said linker polypeptide at said protease cleavage site increases the activity of said reporter.

2. The fusion protein of claim 1, wherein said protease cleavage site is a caspase cleavage site.

3. (Amended) The fusion protein of claim 1, wherein said repressor polypeptide comprises a polypeptide sequence that directs the localization of said fusion protein outside of the nucleus of a cell.

4. The fusion protein of claim 3, wherein said repressor polypeptide is an N-terminal fragment of CD4.

5. The fusion protein of claim 3 wherein said reporter polypeptide is a transcription factor.

6. The fusion protein of claim 5, wherein said transcription factor is C-terminal Lex A-B42 transcription factor.

7. The fusion protein of claim 3, wherein said repressor polypeptide is amyloid precursor protein.

8. The fusion protein of claim 1, wherein said reporter polypeptide is a kinase.